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CLARIFICATION OF THE STRUCTURE OF PERSOONS'S PERIPLANONE-A, AN ARTIFACT DERIVED FROM HAUPTMANN'S PERIPLANONE-A

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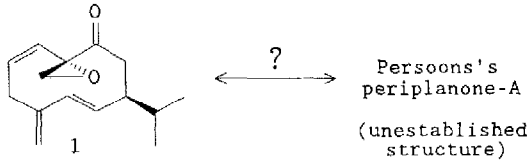
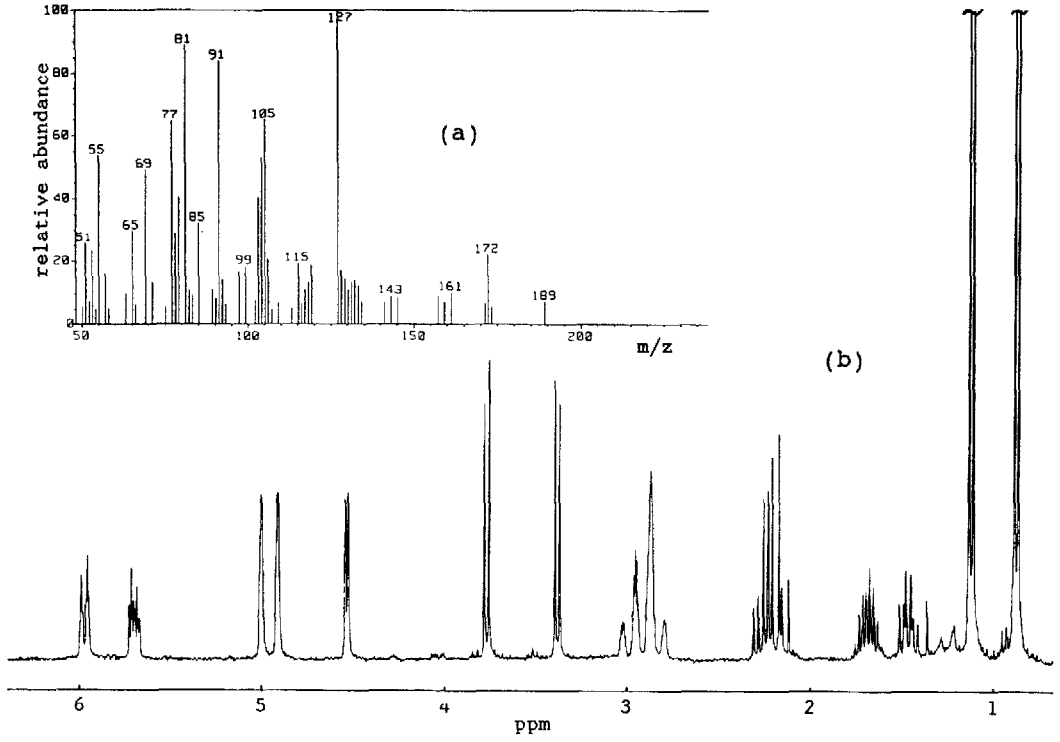
Summary: Thermal rearrangement of Hauptmann's periplanone-A by GLC gave Persoons's periplanone-A, of which structure was determined through an X-ray crystallographic analysis of the corresponding alcohol.

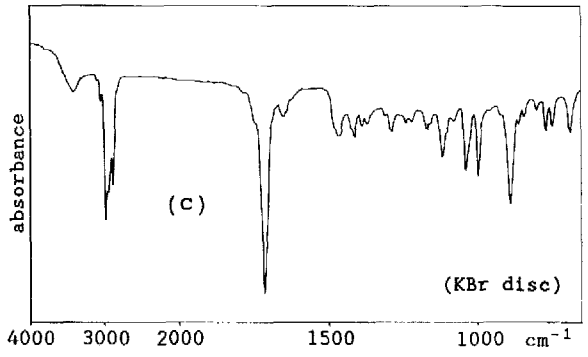
Persoons's periplanone-A is known as a sex pheromone component of the American cockroach, *Periplaneta americana*.[1] In our previous communication we pointed out the problems concerning periplanone-A: (1) the relationship between Hauptmann's periplanone-A 1 and Persoons's periplanone-A, and (2) the structure of Persoons's periplanone-A.[2] We thought that the key to solve the former problem should exist in the different isolation procedures used by each of the research groups. Persoons *et al.*[1] purified periplanone-A finally by GLC, while Hauptmann *et al.*[3] did not expose their sample to such a high temperature. This made us to assume Persoons's periplanone-A to be a thermal rearrangement product of Hauptmann's periplanone-A.[4,5]



We tried first the GC-MS analysis of our synthetic and crystalline Hauptmann's periplanone-A (-)-1[6] at 180°C using a column packed with 3% OV-17. The gas chromatogram showed mainly two peaks. The mass spectrum of the major peak was due to Hauptmann's periplanone-A itself. The minor peak with longer retention time gave the mass spectrum (Fig.1a) which was very similar to that published for Persoons's periplanone-A.[7] In order to isolate the decomposition product, the thermolysis of a total amount of 80 mg of (-)-1 was carried out (condition: column, 3% OV-17, 2m x 6mm at 220°C; injection 260°C; carrier gas, N_2, 45ml/min). Under these conditions, the decomposition was achieved quite efficiently. After TLC purification, the major decomposition product was isolated in 71% yield. Its



δ(300 MHz, CS_2) 0.88 (3H, d, J=6.5Hz), 1.13 (3H, d, J=6.5Hz), 1.47 (1H, dt, J=7.6, 11.0Hz), 1.59-1.79 (1H, m), 2.18 (1H, dd, J=11.0, 16.0Hz), 2.25 (1H, dd, J=7.6, 16.0Hz), 2.78-2.91 (1H, m, J_1=21.6Hz), 2.87 (1H, br), 2.92-3.05 (1H, m, J_1=21.6Hz), 3.38 (1H, d, J=7.6Hz), 3.77 (1H, d, J=7.6Hz), 4.53 (1H, d, J=4.7Hz), 4.91 (1H, br), 5.00 (1H, br), 5.70 (1H, dt, J=3.7, 9.7Hz), 5.96 (br.d, J=9.7Hz)



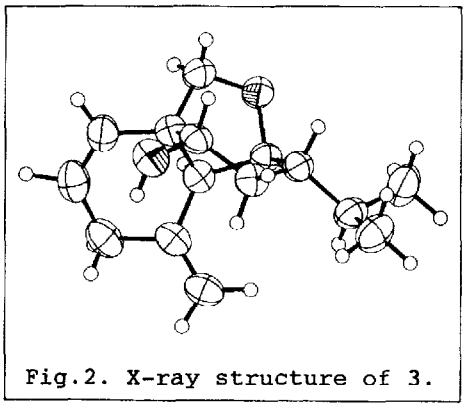
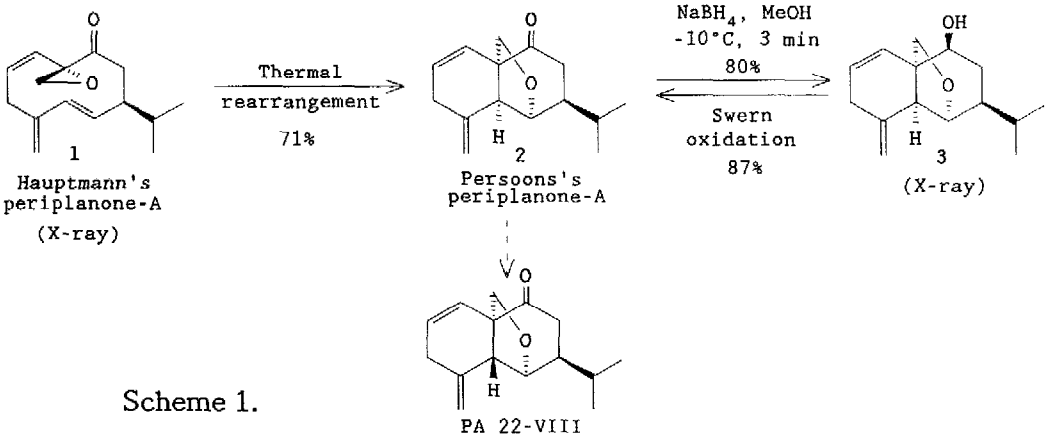


Fig.2. X-ray structure of 3.

Fig.1. (a) Mass, (b) ^{1}H NMR, and (c) IR spectra of the thermal decomposition product of Hauptmann's periplanone-A.



Scheme 1.

^{1}H NMR spectrum (Fig.1b) was identical with that published for Persoons's periplanone-A, although Persoons's sample was contaminated with PA 22-VIII, the stable rearrangement product of Persoons's periplanone-A.[1,2] Furthermore, its IR spectrum (Fig.1c) was exactly the same as that published for Persoons's periplanone-A.[8] Therefore, the major product obtained by thermolysis of Hauptmann's periplanone-A must surely be Persoons's periplanone-A.

Having secured a considerable amoumt of Persoons's periplanone-A, we next attempted its structure determination. On reduction with $NaBH_4$ in MeOH, Persoons's periplanone-A gave a crystalline alcohol (m.p. 77-78°C), whose structure was determined unambiguously to be **3** by an X-ray crystallographic analysis[9] (Fig.2, Scheme 1). The alcohol **3** regenerated in 87% yield Persoons's periplanone-A on Swern oxidation. These results enabled us to establish the structure of Persoons's periplanone-A to be **2**, which was also supported by ^{1}H NMR analyses of **2** and **3**.[10] As mentioned in the previous communication,[2] Shizuri *et al.* proposed **2** for the structure of Persoons's periplanone-A from the reexamination of the spectral data presented by Persoons *et al.*,[11] and quite recently claimed the synthesis of (±)-**2**.[12] However their synthetic product showed an NMR spectrum different from that of Persoons's periplanone-A.[12] Our results implies that the compound synthesized by them was not (±)-**2**, although their structural proposal for Persoons's periplanone-A was correct.

Some comments should be made on the bioactivity and stability of Persoons's periplanone-A **2**. Firstly, our synthetic Persoons's periplanone-A **2** was not active even at 10 μg.[13] The potent activity of **2** reported by Persoons *et al.*[1] therefore seems to be ascribable to the contamination of the highly active pheromone(s), periplanone-B[14] and/or Hauptmann's periplanone-A **1**. Secondly, synthetic Persoons's periplanone-A **2** was quite

stable contrary to Persoons's observation that **2** was unstable (half-life, 2 weeks at 0°C) and gradually changed into PA 22-VIII.[1] Some impurities contained in their sample must have accelerated this conversion.

In conclusion, Persoons's periplanone-A was shown to have no biological activity and to be an artifact derived from Hauptmann's periplanone-A. A lesson learned through whole the works related to Persoons's periplanone-A is that one should employ as mild condition as possible in isolating an unstable bioactive compound to avoid possible decomposition. Production of an artifact may demand tremendous amount of rewardless efforts by others.

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REFERENCES AND NOTES

1. C. J. Persoons, P. E. J. Verwiel, F. J. Ritter and W. J. Nooyen, *J. Chem. Ecol.*, **8**, 439 (1982), and references cited therein.
2. K. Mori and Y. Igarashi, *Tetrahedron Lett.*, **30**, 5145 (1989).
3. H. Hauptmann, G. Mühlbauer and H. Sass, *Tetrahedron Lett.*, **27**, 6189 (1986).
4. The same speculation was made by C. Nishino *et al.*: C. Nishino, K. Kobayashi, M. Fukushima, M. Imanari, K. Nojima and S. Kohno, *Chem. Lett.*, **517** (1988).
5. Dr. Hauptmann also noticed the thermal rearrangement of his periplanone-A to Persoons's. K.M. thanks Drs. Hauptmann, Persoons, and Ritter for this information.
6. S. Kuwahara and K. Mori, to be submitted.
7. E. Talman, P. E. J. Verwiel, F. J. Ritter and C. J. Persoons, *Isr. J. Chem.*, **17**, 227 (1978).
8. C. J. Persoons, "Structure Elucidation of Some Insect Pheromones" (doctoral dissertation), Wageningen, 1977, p.25. We thank Dr. Persoons for his kind gift of this article.
9. We thank Dr. C. Katayama and Mr. H. Inoue of Mac Science Co., Ltd. and also Mr. T. Hori of Rigaku Co. for this analysis. We are grateful to Dr. M. Miyano of Japan Tobacco Inc. for his kind instruction of making the crystals.
10. The NMR studies will be published in detail by M. Mori *et al.*
11. Y. Shizuri, S. Yamaguchi, Y. Terada and S. Yamamura, *Tetrahedron Lett.*, **28**, 1795 (1987).
12. Y. Shizuri, K. Matsunaga and S. Yamamura, *Tetrahedron Lett.*, **30**, 3693 (1989).
13. Persoons's periplanon-A **2** obtained by TLC purification of the crude thermolysis products was bioactive at 10^{-3} μg probably due to the contamination with Hauptmann's periplanone-A **1**. A pure sample of Persoons's periplanone-A, $[\alpha]_D^{25}$ -290° (c=0.096, n-hexane), was prepared by the Swern oxidation of the recrystallized alcohol **3** as shown in Scheme 1. The detailed bioassay results will be published by K. Okada *et al.*
14. S. Kuwahara and K. Mori, *Heterocycles*, **28**, 167 (1989), and references cited therein.

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